REMARKS

Claim 22 has been amended to remove the recitation of "retina." Support for this amendment is found in the specification at, for example, page 14, lines 5-11 and in original claim 9. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l).

Indefiniteness Rejection

Claim 22 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. (Paper No. 20031223 at 2.)

The Examiner stated "[r]egarding claim 22, the limitation 'retina' in line 3 renders the claim indefinite, because generic claim 21 reads on a method for the treatment of a pathology, excluding retinal pathologies. Thus, claim 22 fails to further limit the generic claim."

With a view towards furthering prosecution claim 22 has been amended to remove the limitation "retina." Accordingly, this rejection is rendered moot and should be withdrawn.

Rejections under 35 U.S.C. § 103

Rejection over Louis

Claims 13-20 were rejected under 35 U.S.C. § 103(a) as being obvious over Louis *et al.*, U.S. Patent No. 5,641,750 ("Louis"). (Paper No. 20031223 at 2). For the reasons presented below, reconsideration and withdrawal of the rejection respectfully is solicited.

Louis "relates generally to methods for treating injury or degeneration of retinal neurons, and in particular photoreceptors, by administering glial cell line-derived neurotrophic factor (GDNF)." (Abstract).

In making the rejection, the Examiner relied on Louis for disclosing "a method for treating pathologies leading to vision loss comprising administering the neurotrophic factor GDNF (See col. 6, lines 5-20)." (Paper No. 20031223 at 3). The Examiner stated "[w]ith regard to claim 13, 16 and 17, the patent includes inherited retinal degenerations, age-related macular degeneration, diabetic retinopathy and surgery-induced retinopathies among the pathologies treated by the method of the invention (See col. 6, lines 55 to col. 7, line 3)." (*Id.*). The Examiner further stated "[t]he nerve growth factor claimed by Applicant is part of the neurotrophic factor family disclosed by the patent (See col. 1, line 55 to col. 2, line 65)." (*Id.*). The Examiner further stated "[w]ith regard to the amount of nerve growth factor claimed by Applicant, the patent discloses an intraocular dose of 0.001-10 mg/day (See col. 20, lines 42-51)." (*Id.*).

The Examiner acknowledged that "[t]he patent does not specifically teach a dosage in microgram/ml, as claimed by Applicant." (*Id.*). The Examiner stated "however, the patent teaches that the specific dose may be calculated by one of ordinary skill in the art in view of the body weight and organ size (See col. 20, lines 32-51)." (*Id.*).

The Examiner then stated "[w]ith regard to the limitation that the nerve growth factor passes through the external tissues to the internal tissues of the eye, the patent contemplates extraocular administration of the composition between the eyeball and the eyelid, as well as intraocular administration, and teaches the inclusion of an agent in topically applied ophthalmic compositions to promote the penetration or transport of the therapeutic agent into the eye (See col. 17, line 61 to col. 18, line 47)." (*Id.*).

The Examiner then stated:

- "[w]ith respect to claim 14, 18 and 19, the patent discloses formulations in the form of ophthalmic solutions, suspensions and ointments (See col. 17, lines 50-54)." (*Id.*).
- "[r]egarding claim 15, the patent provides ocular inserts, implants and sustained-release polymeric formulations (See col. 19, line 50 to col. 20, line 17)." (*Id.* at 3).
- "[w]ith regard to claim 20, the patent discloses natural GDNF isolated from mammalian cells as well as recombinant GDNF (See col. 8, lines 9-62)." (*Id.*).

The Examiner concluded that:

> "it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of Louis to [devise] a method for the treatment of a pathology affecting the internal tissues of the eye, comprising administering a nerve growth factor. The expected result would have been a successful method of treatment. Because of the teachings of Louis, that the ophthalmic compositions of the invention may be applied to treat retinal degenerations, one of ordinary skill in the art would have a reasonable expectation that the method claimed in the instant application would be successful in treating ocular disorders. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made." (*Id.*).

It is well settled that the Examiner bears the burden to set forth a *prima facie* case of unpatentability. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002); *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); and *In re Piasecki*, 223 USPQ 785, 788 (Fed. Cir. 1984). If the PTO fails to meet its burden, then the applicant is entitled to a patent. *In re Glaug*, 62 USPQ2d at 1152. Moreover, in attempting to set forth a *prima facie* case for obviousness the Examiner is required to consider the claimed invention as a whole (i.e., consider each and every

limitation of the claimed invention). "In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983)." (MPEP § 2141.02, 8th ed., Rev. 1, February 2003, p. 2100-120.) (Emphasis original.)

Initially, we note with regard to claims 13, 16, and 17, the Examiner failed to engage in the mandatory analysis handed down by the Supreme Court and adopted as PTO policy. For example, the rejection failed to consider claims 13, 16, and 17 as a whole. The rejection failed to identify the differences between each of claims 13, 16, and 17 and the cited documents. And, the rejection failed to engage in any analysis relating to whether the claimed invention as a whole would have been obvious. That was error. *See Graham v. John Deere Co.*, 383 US 1, 17-18, 148 USPQ 459, 467 (1966); and MPEP §2141 at 2100-115 ("Office policy is to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 USC §103."); and *Ex Parte Roller*, 2004 WL 45458, *2 (unpublished) (BPAI 2004) ("In rejecting claims under 35 U.S.C. §103, it is incumbent upon the Examiner to establish a factual basis to support the legal conclusion of obviousness. In doing so, the Examiner is expected to make the factual determinations set forth in *Graham v. John Deere Co.*, and to provide a reason why one having ordinary skill in the art would have been led to modify the prior art or to combine prior art references to arrive at the claimed invention.") (citations omitted). For this reason alone, the rejection should be withdrawn.

We further note that Louis is the parent application of Louis *et al.*, U.S. Patent No. 5,736,516, which was cited against the applicant in the first Office Action (Paper No. 6 at p.

3) in a 35 U.S.C. § 102(e) rejection by the Examiner. After reviewing our Response filed March 27, 2003, the Examiner withdrew the rejection in its entirety. The grounds on which the Examiner withdrew the rejection were simply that the "prior art teaches GDNF, which is different from the nerve growth factor claimed by Applicant." *See* Paper No. 9 at 5. In other words, the disclosure of Louis had already been considered as a reference in the first Office Action in respect of this application. In view of the arguments made, the Examiner ***conceded*** that Louis does not "teach[] ... the nerve growth factor claimed by Applicant," and the rejection had been withdrawn. For this additional reason, the current rejection, based on the same disclosure, should be withdrawn.

As discussed in our earlier response, is respectfully submitted that the Examiner has misinterpreted the disclosure of Louis. As the Examiner has previously acknowledged, Louis does not "teach[] ... the nerve growth factor claimed by Applicant." In particular, Louis does not disclose the use of nerve growth factor (NGF). Louis is concerned with the treatment of retinal affections, and diseases affecting the optic nerve, based on the use of another "growth factor:" Glial Cell Line-Derived Neurotrophic Factor (GDNF). GDNF is a biologically active agent which is very different from NGF, having no features in common therewith but the fact that they both belong to the large family of neurotrophic factors. NGF and GDNF have completely different structures, bind to different receptors, and have different biological actions.

Louis discloses one large genus of neurotropic factors (see col. 1, line 20 to col. 2, line 50) and then specifically discusses methods for treating injury or degeneration of retinal neurons, and in particular photoreceptors, by administering GDNF. Louis contains no disclosure or teaching which would lead one of ordinary skill in the art to select NGF for use in treating internal pathologies of the eye.

As is well settled, a broad genus does not render obvious a species or subgenus contained therein. *See, e.g., In re Baird*, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994); *see also* MPEP § 2144.08 (8th Ed., Rev. 1, February 2003, p. 2100-141). To support a *prima facie* case of obviousness, a cited document must provide motivation for one of ordinary skill in the art to select the claimed species to arrive at the claimed invention. *See* MPEP § 2144.08 (p. 2100-143). [1]

NGF more properly belongs to the family of neurotrophins (see from col. 1, line 55 to col. 2, line 6), while GDNF belongs to the family of neurokines and is more similar in structure to Transforming Growth Factor-b (TGF-b) (see col. 2, lines 16-28). The GDNF family is characterized by the binding to a specific receptor, RET, completely different (in terms of structure, mechanism of function and activity) from the p75 and Trk receptors that bind to the neurotrophin family (e.g. NGF). For example, GDNF exerts a potent neurotrophic effect on dopaminergic neurons both in vitro and in vivo (see, e.g., Lin L.F.H. et al., Science 260:1130-2, 1993, cited in Yan et al. U.S. Patent No. 5,641,749), while NGF does not act on these neurons (Granholm A.C. et al., Exp. Brain Res. 116:29-38, 1997). [2]

In view of the foregoing, it is clear that the method disclosed by Louis for treating retinal affections and diseases affecting the optic nerve with GDNF is substantially different from the claimed method of administering NGF "over the ocular surface of a subject in need thereof, wherein said nerve growth factor passes through the external tissues of said eye to said

[1] Office personnel should determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, i.e. to select the claimed species or subgenus from the disclosed prior art genus. See *Deuel*, 51 F.3d at 1557, 34 USPQ2d at 1214 ("[A] *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art.") (Emphasis original to *Deuel*.).

[2] These references are presently unavailable to applicant's attorneys. If the Examiner wishes to obtain copies, please contact the undersigned who will ensure that they are made available.

internal tissues." "Even when obviousness is based on a single reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference." *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000). In the present case, the Examiner has adduced no evidence to support the conclusion that it would have been obvious "to apply the teachings of Louis to [devise] a method for the treatment of a pathology affecting the internal tissues of the eye, comprising administering a nerve growth factor." (Paper No. 20031223 at 4). While the Examiner states, as quoted above, that "[b]ecause of the teachings of Louis, that the ophthalmic compositions of the invention may be applied to treat retinal degenerations, one of ordinary skill in the art would have a reasonable expectation that the method claimed in the instant application would be successful in treating ocular disorders," no evidence is cited in support of this statement. *Id.* Thus, the rejection is factually and legally deficient, and it is respectfully requested that it be reconsidered and withdrawn.

In addition, Louis clearly suggests that NGF and GDNF are not biologically equivalent and cannot be used one for the other or in conjunction with each other in the therapy of ophthalmic disorders. For instance, Louis discloses, at col. 5, lines 3-12, a number of therapeutic agents and, specifically, growth factors that may be added to GDNF in a therapeutic combination for treating retinal disorders. ***None of these agents comprise NGF.***

Further, the same document reports that administration of NGF "had no effect" on the photoreceptor survival in the light-damaged model in albino rats, thereby suggesting that NGF – contrary to other "growth factors" – is not effective in the treatment of retinal disorders (see col. 4, lines 5-20). To the extent the Examiner suggests that the GDNF disclosed in Louis may be omitted completely in favor of a NGF, we note that such a basis for unpatentability is contrary to binding precedent. It is well settle that to do what a reference teaches against is the

antithesis of obviousness. *See, e.g., In re Buehler*, 185 USPQ 781, 786-87 (CCPA 1975) and *In re Rosenberger*, 156 USPQ 24, 26 (CCPA 1968). For this additional reason, the rejection should be withdrawn.

In addition, the Examiner completely ignored the claimed range limitation of "10 to 500 μg/ml." The Examiner stated that "[t]he patent does not specifically teach a dosage in microgram/ml, as claimed by Applicant," but "the patent teaches that the specific dose may be calculated by one of ordinary skill in the art in view of the body weight and organ size (See col. 20, lines 32-51)." (Paper No. 20031223 at 3). However, the Examiner has offered no evidence to support that one of ordinary skill in the art would arrive at the applicant's claimed range from the general disclosure in Louis that "[t]he specific dose may be calculated by one of ordinary skill in the art in view of the body weight and organ size." See col. 20, lines 32-33. A *prima facie* case for obviousness requires the Examiner to demonstrate that each and every element recited in the claim is found in the prior art reference(s). *See*, again, MPEP § 2143.03 at 2100-128, 8th Ed. Rev. 1 (Feb. 2003) ("All Claim Limitations Must Be Taught or Suggested"); *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) (To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art.). Further, the general disclosure relied upon by the Examiner does not even pertain to dosing amounts for NGF. The disclosure is referring to the pharmacokinetic properties of GDNF, which, as discussed above, is a completely different biologically active agent than NGF. For this additional reason, the rejection should be withdrawn.

In making the rejection as to claims 14, 18, and 19, the Examiner asserted only that "[w]ith respect to claim 14, 18 and 19, the patent discloses formulations in the form of ophthalmic solutions, suspensions and ointments (See col. 17, lines 50-54)." (Paper No.

20031223 at 3). As is well settled, if an independent claim is not obvious under 35 U.S.C. § 103, then any claim depending therefrom is not obvious. *Hartness International, Inc. v. Simplimatic Engineering Co.*, 2 USPQ2d 1826, 1831 (Fed. Cir. 1987) ("*A fortiori*, dependent claim 3 was nonobvious (and novel) because it contained all the limitations of claim 1 plus a further limitation."). Accordingly, the rejection of claims 14, 18, and 19 must be withdrawn for the reasons set forth above in relation to the rejection of claim 13, from which claims 14, 18, and 19 ultimately depend.

A *prima facie* case for obviousness requires the Examiner to demonstrate that each and every element recited in the claim is found in the prior art reference(s). See MPEP § 2143.03 at 2100-128, 8th ed. Rev. 1, February 2003 ("All Claim Limitations Must Be Taught or Suggested"); *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) (To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art.). By statute "a dependent claim is construed to incorporate by reference all the limitations of the claim to which it refers." 35 U.S.C. § 112. The Examiner made no reference to his earlier argument as to claim 13 (or claim 16 or claim 17). Accordingly, the rejection failed to account for any of the limitations of claim 13 from which claims 14, 18, and 19 ultimately depend. Instead, the Examiner asserted only that the further limitations recited in claims 14, 18 and 19 are disclosed by Louis. Thus, the Examiner has not even considered each and every element of claims 14, 18, and 19. Because the Examiner hasn't even asserted that each and every element of claim 14, 18, and 19 are found in Louis, the rejection fails to present a *prima facie* case under 35 U.S.C. § 103. For this additional reason, the rejection should be withdrawn.

In making the rejection as to claim 15, the Examiner asserted only that "[r]egarding claim 15, the patent provides ocular inserts, implants and sustained-release

polymeric formulations (See col. 19, line 50 to col. 20, line 17)." (Paper No. 20031223 at 3). As noted above, if an independent claim is not obvious under 35 U.S.C. § 103, then any claim depending therefrom is not obvious. *Hartness*, 2 USPQ2d at 1831. Accordingly, the rejection of claim 15 must be withdrawn for the reasons set forth above in relation to the rejection of claim 13, from which claim 15 depends.

Moreover, there is a "burden of proof on the Patent Office which requires it to produce the factual basis for its rejection of an application under sections 102 and 103. . . ." *In re Warner*, 154 USPQ 173, 177 (CCPA 1967). Examiner supposition or belief is not enough to support a rejection. That, however, is all that is offered here.

In making the rejection as to claim 20, the Examiner asserted only that "[w]ith regard to claim 20, the patent discloses natural GDNF isolated from mammalian cells as well as recombinant GDNF (See col. 8, lines 9-62)." (*Id.*). Because claim 20 depends from claim 13, the rejection of claim 20 must be withdrawn for the reasons set forth above in relation to the rejection of claim 13.

In light of the forgoing, it is respectfully submitted that the rejection over Louis has been rendered moot and should be withdrawn.

Rejection over Glaser

Claims 21-24 were rejected under 35 U.S.C. § 103(a) as being obvious over Glaser *et al.*, U.S. Patent No. 5,767,079 ("Glaser").

Glaser discloses "a method for the treatment of ophthalmic disorders. The method is suitable for treatment of a variety of disorders including macular holes, macular degeneration, and retinal detachment and tears, cataracts, and corneal and scleral injuries. The

method entails application of an effective amount of Transforming Growth Factor-β (TGF-β) to the affected region." (Abstract.)

In making the rejection, the Examiner relied on Glaser for disclosing "a method for the treatment of ophthalmic disorders, comprising administering a composition comprising nerve growth factor (See col. 8, lines 45-58 and col. 11, lines 62-67)." (Paper No. 20031223 at 4).

The Examiner stated "[w]ith regard to claims 21-23, the patent includes disorders of the cornea and sclera, Sjogren's syndrome, an autoimmune disease, and corneal neovascularization due to trauma among the diseases treated by the method of the invention (See col. 8, line 54 to col. 9, line 18)." (*Id.* at 5).

The Examiner acknowledged that "[t]he patent does not specifically teach that the nerve growth factor passes through the external tissues to the internal tissues of the eye." (*Id.*). The Examiner stated, however, that:

> "The patent teaches that the composition of the invention may be administered by different routes, including intraocular, subretinal, intrascleral and subconjuctival injection, depending on the nature and location of the pathology (See col. 10, lines 45-49). Thus, one of ordinary skill in the art would have been capable of determining the best route of administration into the eye, so that the active agent would reach the internal tissues of the eye." (*Id.*).

The Examiner then stated

> "[w]ith respect to claim 24, the patent does not specifically disclose the amount of nerve growth factor in the composition of the invention, however, the patent teaches that the formulations, method of administration and dosage depend upon the disorder to be treated and the history of the patient, and these factors are readily determinable during therapy (See col. 10, lines 25-35). Thus, one of ordinary skill in the art would have been able to determine the optimal dosage according to the disease to be treated and the condition of the patient." (*Id.*).

The Examiner then concluded that:

> "it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of Glaser et al. to device a method for the treatment of a pathology affecting the internal tissues of the eye, comprising administering a nerve growth factor. The expected result would have been a successful method of treatment. Because of the teachings of Glaser et al., that ophthalmic compositions comprising nerve growth factors may be applied to treat ophthalmic disorders, including those affecting the cornea and sclera, one of ordinary skill in the art would have a reasonable expectation that the method claimed in the instant application would be successful in treating ocular disorders. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made." (*Id.* at 5-6).

Initially, we note with regard to claims 21, 22, and 23, the Examiner failed to engage in the mandatory obviousness analysis handed down by the Supreme Court and adopted as PTO policy. For example, the rejection failed to consider claims 21, 22, and 23 as a whole. The rejection failed to identify the differences between each of claims 21, 22, and 23 and the cited documents. And, the rejection failed to engage in any analysis relating to whether the claimed invention as a whole would have been obvious. That was error. *See Graham v. John Deere Co.*, 383 US 1, 17-18, 148 USPQ 459, 467 (1966); and MPEP §2141 at 2100-115 ("Office policy is to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 USC §103."); and *Ex Parte Roller*, 2004 WL 45458, *2 (unpublished) (BPAI 2004) ("In rejecting claims under 35 USC §103, it is incumbent upon the Examiner to establish a factual basis to support the legal conclusion of obviousness. In doing so, the Examiner is expected to make the factual determinations set forth in *Graham v. John Deere Co.*, and to provide a reason why one having ordinary skill in the art would have been led to modify

the prior art or to combine prior art references to arrive at the claimed invention.") (citations omitted).

Obviousness ***must*** be based upon facts, "cold hard facts." In re Freed, 165 USPQ 570, 571-72 (CCPA 1970). When a conclusion of obviousness is not based upon facts, it cannot stand. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993). Further, "to establish *prima facie* obviousness of a claimed invention, ***all claim limitations*** must be taught or suggested by the prior art." MPEP § 2143.03 citing *In re Royka*, 180 USPQ 580 (CCPA 1974).

Here, Glaser discloses a method for the treatment of ophthalmic disorders by administering Transforming Growth Factor-β (TGF-β). A person of ordinary skill in the art would immediately recognize that TGF-β and NGF represent two completely different molecules with different origin, different biochemical and biological characteristics, different receptors, different mechanisms, and different effects.

The NGF biological pathway is completely different from the biological pathway of TGF-β; they have different receptors and different transcription factors. TGF-β elicits its cellular responses through formation of heteromeric complexes of specific type I and type II serine/threonine kinase receptors (TGF-β-RI and TGF-β-RII). TGF-β-RII is a constitutively active kinase, which, upon binding to the ligand, initiates the signaling cascade that involves phosphorylation of the TGF-β-RI, and the propagation of the signal by Smad2 and Smad3. Activated phosphorylation then leads to nuclear translocation of these transcription factors and subsequent trans-activation of several target genes. Smad proteins transduce TGF-β signals from the cell surface to the nucleus, regulating a variety of physiologic processes. In the nucleus, Smads control gene expression by a direct binding to both DNA and transcription factors. Individual Smads regulate distinct subsets of target genes (see Derynck R. and Feng X.H. *TGF-*

beta receptor signaling, Biochim Biophys Acta. 1997; 1333(2): F105-150; Massague J., et al. *TGF-beta receptors*, Mol Reprod Dev. 1992; 32(2): 99-104; Padgett R.W., Savage C., and Das P. *Genetic and biochemical analysis of TGF beta signal transduction*, Cytokine Growth Factor Rev. 1997; 8(1): 1-9; Padgett R.W., Das P., and Krishna S. *TGF-beta signaling, Smads, and tumor suppressors*, Bioassays. 1998; 20(5): 382-390)[3].

Moreover, TGF-β is characterized by its activity on mesodermal derived cells, such as fibroblasts, with proliferative and fibrogenic activity; whereas, NGF is characterized by its activity on ectodermal derived cells, such as neurons, with trophic and differentiative activity, but not proliferative activity. Indeed, when the activity of TGF-β on the immune system was discovered, it was demonstrated that such activity is produced by the Th3 subset lymphocytes exerting an immune suppression, while the activity of NGF is produced by Th2 lymphocytes exerting a role in allergic reaction.

It is respectfully submitted that the Examiner has misstated the disclosure of Glaser. In the entire disclosure of Glaser, NGF is only mentioned once. Glaser states generally that "[o]ther growth factors which have both wound healing and neurotrophic effects *can be applied in certain of these inventive treatments*. These factors include, but are not limited to, acidic and basic fibroblast growth factor, insulin, insulin-like growth factor, platelet-derived growth factor, *nerve growth factor*, epidermal growth factor, transforming growth factor-α, colony-stimulating factor, keratinocyte growth factor, and tissue plasminogen activator." Col. 11, line 62 to col. 12, line 2 (emphasis added). Glaser says nothing about the claimed method of treating pathologies affecting the internal tissues of the eye "comprising nerve growth factor over

[3] These references are presently unavailable to applicant's attorneys. If the Examiner wishes to obtain copies, please contact the undersigned who will ensure that they are made available.

the ocular surface of a subject in need thereof, wherein said nerve growth factor passes through the external tissues of said eye to said internal tissues." Glaser only discloses that "[o]ther growth factors which have both wound healing and neurotrophic effects *can be applied in certain of these inventive treatments"* and then discloses a laundry list of factors.

Simply put, this general statement falls short of the requisite suggestion and/or motivation to arrive at the applicant's claimed method. "Even when obviousness is based on a single reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference" to arrive at the applicant's claimed invention. *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000). The Federal Circuit instructs that "[t]he mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, 972 F.2d 1260, 1266 n.14, 23 USPQ2d 1780, 1783- 84 n.14 (Fed. Cir. 1992). For this reason alone, the rejection should be withdrawn.

To appreciate the completely different nature of NGF and TGF-β, it may be useful to review a paper by Schuldiner *et al.*, *Effects of eight growth factors on the differentiation of cells derived from human embryonic stem cells*, (PNAS, 97(21):11307-12, October 10, 2000)[4]. The paper evaluates the effects of eight growth factors on human embryonic stem cells. This paper demonstrates the completely different differentiative effects of NGF and TGF-β. Regarding NGF and TGF-β, the authors conclude by classifying them in two different subsets of growth factors (see page 11311, left col., last paragraph).

[4] A copy of this article is enclosed as Exhibit 1.

The foregoing demonstrates that a person of ordinary skill in the art would not have considered it obvious to use NGF on the basis of data discussing TGF-β. Also, it should be borne in mind that the "growth factor" suffix that the concerned agents have in common is only due to the fact that, historically, this definition was attached to any endogenous molecule affecting cell proliferation, independent of the target cell.

Moreover, with reference to Glaser, the Examiner states that "the patent teaches that the composition of the invention may be administered by different routes, ..." and that as a consequence "one of ordinary skill in the art would have been ***capable of determining*** the best route of administration into the eye, so that the active agent would reach the internal tissues of the eye." (Paper No. 20031223 at 5) (emphasis added). However, the passage relied upon by the Examiner (col. 10, lines 45-55) mentions six types of injection in the various ocular tissues, as well as intra venous injection, subcutaneous injection, and oral administration, ***but does no mention topical application over the ocular surface***. Based on this disclosure, one of ordinary skill in the art would not have concluded that NGF can be administered over the ocular surface of a subject (e.g., eye-drop) so that NGF passes through the external tissues of the eye to the internal tissues in order to treat pathologies affecting the internal tissues of the eye.

Further, the Examiner's argument that one of ordinary skill in the art would have been ***capable of determining*** the best route of administration into the eye ..." has been expressly rejected by the Board. *See, e.g., Ex parte Levengood*, 28 USPQ2d 1300, 1302 (B.P.A.I. 1993) ("At best, the examiner's comments regarding obviousness amount to an assertion that one of ordinary skill in the relevant art ***would have been able to arrive*** at appellant's invention because he had the necessary skills to carry out the requisite process steps. This is an inappropriate

standard for obviousness. That which is ***within the capabilities*** of one skilled in the art is not synonymous with obviousness.") (emphasis added)(citation omitted).

One of ordinary skill does not pick and choose elements merely because they are "capable." One of ordinary skill does not make substitutions for the sake of it, or merely because something might be "capable." One of ordinary skill follows teachings or suggestions that one ***should*** deviate from the disclosure of a reference, teachings or suggestions which would have ***"strongly motivated"*** one to arrive at the claimed method for the treatment of a pathology affecting the internal tissues of the eye by administering "a composition comprising nerve growth factor over the ocular surface of a subject in need thereof, ***wherein said nerve growth factor passes through the external tissues of said eye to said internal tissues"*** [See Ex parte Graselli, 231 USPQ 393, 394 (Bd. App. 1983)], the type of motivation that would have ***"impelled"*** one to do so [*See Ex parte Levengood*, 28 USPQ2d 1300, 1302 (B.P.A.I. 1993)], or the type of suggestion that the selection and combination ***"should"*** be made [*See Ex parte Markowitz*, 143 USPQ 303, 305 (Bd. App. 1964)]. That is what a conclusion of obviousness requires. *See*, again, *Levengood*, 28 USPQ2d at 1302.

"Capable of determining" falls far short of the requisite suggestion or motivation which would have led one to deviate from Glaser and rebuild the Glaser method so that one would have arrived at what is claimed. Because something is simply "capable" is not the stuff of an obviousness rejection. The Examiner's ***"capable of determining"*** argument is not supported by the facts or the law. Should the rejection be maintained it respectfully is requested that the Examiner provide authority that would support the argument that "one of ordinary skill in the art would have been ***capable of determining*** the best route of administration into the eye, so that the

active agent would reach the internal tissues of the eye" is sufficient to establish obviousness. (Paper No. 20031223 at 5).

In making the rejection as to claim 24, the Examiner asserted only that "[w]ith respect to claim 24, the patent does not specifically disclose the amount of nerve growth factor in the composition of the invention, however, the patent teaches that the formulations, method of administration and dosage depend upon the disorder to be treated and the history of the patient, and these factors are readily determinable during therapy (See col. 10, lines 25-35). Thus, one of ordinary skill in the art would have been able to determine the optimal dosage according to the disease to be treated and the condition of the patient." (Paper No. 20031223 at 5).

As is well settled, if an independent claim is not obvious under 35 U.S.C. § 103, then any claim depending therefrom is not obvious. *Hartness International, Inc. v. Simplimatic Engineering Co.*, 2 USPQ2d 1826, 1831 (Fed. Cir. 1987). Accordingly, the rejection of claim 24 must be withdrawn for the reasons set forth above in relation to the rejection of claim 21, from which claim 24 depends.

Rejection over Yan

Claims 25-36 are rejected under 35 U.S.C. § 103(a) as being obvious over Yan *et al.*, U.S. Patent No. 5,641,749 ("Yan"). (Paper No. 20031223 at 6).

Yan "relates generally to methods for treating injury or degeneration of retinal ganglion cells by administering glial cell line-derived neurotrophic factor (GDNF). The invention relates specifically to methods for treating optic nerve injury or degeneration associated with glaucoma." (Abstract).

In making the rejection, the Examiner relied on Yan for disclosing "a method for treating injury or degeneration of retinal ganglion cells comprising administering the neurotrophic factor GDNF (See col. 4, lines 55-67)." (Paper No. 20031223 at 6).

Initially, we note with regard to claims 25, 28, 29 and 33-36, the Examiner failed to engage in the mandatory analysis handed down by the Supreme Court and adopted as PTO policy. For example, the rejection failed to consider claims 25, 28, 29 and 33-36 as a whole. The rejection failed to identify the differences between each of claims 25, 28, 29 and 33-36 and the cited documents. And, the rejection failed to engage in any analysis relating to whether the claimed invention as a whole would have been obvious. That was error. *See Graham v. John Deere Co.*, 383 US 1, 17-18, 148 USPQ 459, 467 (1966); and MPEP §2141 at 2100-115 ("Office policy is to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 USC §103."); and *Ex Parte Roller*, 2004 WL 45458, *2 (unpublished) (BPAI 2004) ("In rejecting claims under 35 USC §103, it is incumbent upon the Examiner to establish a factual basis to support the legal conclusion of obviousness. In doing so, the Examiner is expected to make the factual determinations set forth in *Graham v. John Deere Co.*, and to provide a reason why one having ordinary skill in the art would have been led to modify the prior art or to combine prior art references to arrive at the claimed invention.") (citations omitted).

Furthermore, it is respectfully submitted that the Examiner has misinterpreted the disclosure of Yan. Yan does not disclose or suggest "[a] method for the treatment or prophylaxis of a pathology affecting the internal tissues of an eye, comprising the administration of a composition comprising from 200 to 500 μg/ml of nerve growth factor over the ocular surface of a subject in need thereof, wherein said nerve growth factor passes through the external tissues of

said eye to said internal tissues." Yan is concerned only with treating injury or degeneration of retinal ganglion cells and optic nerve injury or degeneration based on the use of Glial Cell Line-Derived Neurotrophic Factor (GDNF). As discussed above, in regards to the rejection over Louis, GDNF is a biologically active agent very different from NGF, having no features in common therewith but the fact that they both belong to the large family of neurotrophic factors. NGF and GDNF have completely different structures, bind to different receptors, and have different biological actions.

Like Louis, Yan simply discloses one large genera of neurotropic factors (see col. 1, line 12 to col. 2, line 23) and then specifically discusses methods for treating injury or degeneration of retinal ganglion cells by administering GDNF. Yan contains no disclosure or teaching which would lead one of ordinary skill in the art to select NGF for use in treating internal pathologies of the eye.

The disclosure of a broad genus does not per se render obvious a species or subgenus contained therein. *See, e.g., In re Baird*, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994); *see also* MPEP § 2144.08 (8th Ed., Rev. 1, February 2003, p. 2100-141). To support a *prima facie* case of obviousness, a cited document must provide motivation for one of ordinary skill in the art to select the claimed species to arrive at the claimed invention. See MPEP § 2144.08 (p. 2100-143).[5]

As discussed above, NGF more properly belongs to the family of neurotrophins (see col. 1, lines 43-54), while GDNF belongs to the family of neurokines and is more similar in

[5] "Office personnel should determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, i.e. to select the claimed species or subgenus from the disclosed prior art genus. See *Deuel*, 51 F.3d at 1557, 34 USPQ2d at 1214 ("[A] *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art.") (Emphasis original to *Deuel*.).

structure to Transforming Growth Factor-β (TGF-β) (see col. 1, from line 5 to col. 2, line 41). The GDNF family is characterized by the binding to a specific receptor, RET, completely different (in terms of structure, mechanism of function and activity) from the p75 and Trk receptors that bind to the neurotrophin family (e.g. NGF). For example, GDNF exerts a potent neurotrophic effect on dopaminergic neurons both in vitro and in vivo (see, e.g., Lin L.F.H. et al., Science 260:1130-2, 1993, cited in Yan), while NGF does not act on these neurons (Granholm A.C. et al., Exp. Brain Res. 116:29-38, 1997).[6]

In view of the foregoing, it is clear that the method disclosed by Yan of using GDNF to treat optic nerve injury or degeneration associated with glaucoma is substantially different than the claimed method "for the treatment or prophylaxis of a pathology affecting the internal tissues of an eye, comprising the administration of a composition ***comprising from 200 to 500 μg/ml of nerve growth factor over the ocular surface of a subject in need thereof, wherein said nerve growth factor passes through the external tissues of said eye to said internal tissues.***" "Even when obviousness is based on a single reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference." *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000). In the present case, the Examiner has provided no evidence to support the conclusion that it would have been obvious "to apply the teachings of Yan to devi[s]e a method for the treatment of a pathology affecting the internal tissues of the eye, comprising administering a nerve growth factor." (Paper No. 20031223 at 7). While the Examiner states, as quoted supra, that "[b]ecause of the teachings of Yan et al, that the ophthalmic compositions of the invention may be applied to treat glaucoma,

[6] These references are presently unavailable to applicant's attorneys. If the Examiner wishes to obtain copies, please contact the undersigned who will ensure that they are made available.

one of ordinary skill in the art would have a reasonable expectation that the method claimed in the instant application would be successful in treating ocular disorders," no evidence is cited in support of this statement. *Id.* Thus the rejection is factually and legally deficient, and it is respectfully requested that it be reconsidered and withdrawn.

In addition, the Examiner completely ignored the claimed range limitation of "200 to 500 μg/ml." The Examiner stated "[w]ith regard to the amount of nerve growth factor claimed by Applicant, the patent teaches that the specific do[se] ***may be calculated according to body weight and organ size, and is routinely made by those of ordinary skill in the art*** (See col. 18, line 58 to col. 10 [sic])." (Paper No. 20031223 at 6) (emphasis added). However, the Examiner has offered no evidence to support that one of ordinary skill in the art would arrive at the applicant's claimed range from the general disclosure in Yan that "the specific dose may be calculated according to considerations of body weight, body surface area or organ size." See col. 18, lines 58-59. A *prima facie* case for obviousness requires the Examiner to demonstrate that each and every element recited in the claim is found in the prior art reference(s). See, again, MPEP § 2143.03 at 2100-128, 8th Ed. Rev. 1 (Feb. 2003) ("All Claim Limitations Must Be Taught or Suggested"); *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) (To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art.). Further, the general disclosure relied upon by the Examiner does not even pertain to dosing amounts for NGF. The disclosure is referring to the pharmacokinetic properties of GDNF, which as discussed above is a completely different biologically active agent than NGF. For this additional reason, the rejection should be withdrawn.

In making the rejection as to claims 26, 30, and 31, the Examiner asserted only that "[w]ith respect to claims 26, 30 and 31, the patent discloses formulations in the form of

ophthalmic solutions, suspensions and ointments (See col. 16, line 6-10)." (Paper No. 20031223 at 7). As noted above, if an independent claim is not obvious under 35 U.S.C. § 103, then any claim depending therefrom is not obvious. *Hartness*, 2 USPQ2d at 1831. Accordingly, the rejection of claims 26, 30, and 31 must be withdrawn for the reasons set forth above in relation to the rejection of claim 25, from which claims 26, 30, and 31 ultimately depend.

In making the rejection as to claim 27, the Examiner asserted only that "the patent provides ocular inserts, implants and sustained-release polymeric formulations (See col. 18, lines 39-55)." (Paper No. 20031223 at 7). This rejection must be withdrawn for the same reasons that the rejection of claim 25, from which claim 27 depends, must be withdrawn.

Similarly, in making the rejection as to claim 32, which depends from claim 25, the Examiner asserted only that "the patent discloses natural GDNF isolated from mammalian cells as well as recombinant GDNF (See col. 6, lines 38-51)." (Paper No. 20031223 at 7). Accordingly, the rejection of claim 32 must be withdrawn for the reasons set forth above in relation to the rejection of claim 25.

CONCLUSION

In view of the foregoing, favorable action on the merits, including entry of the amendments, withdrawal of the rejections, and allowance of all the claims, are respectfully requested. If the Examiner has any questions regarding this paper, please contact one of the undersigned attorneys.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on June 30, 2004.

N. Whitney Wilson, Reg. No. 38,661

Respectfully submitted,

By: _____

N. Whitney Wilson
Registration No. 38,661
Charles M. Avigliano
Registration No. 52,578
BRYAN CAVE LLP
1290 Avenue of the Americas
33rd Floor
New York, NY 10104-3300
Phone: (212) 541-2000
Fax: (212) 541-4630